LOUIS STOKES CLEVELAND VA MEDICAL CENTER

Medical Research Service

Standard Operating Policy and Procedure (SOP)

Effective Date: June 2, 2022

SOP Title: Sponsor Adverse Event/Unanticipated Problems Reporting - Device

SOP Number: Human Researchers – HSP-023

SOP Version: .02

1. Purpose.

To establish the requirements and procedures for reporting of adverse experiences occurring at clinical sites, and to fulfill regulatory and ethical responsibilities of study staff.

2. Policy

This document applies to non-exempt human subjects' research conducted by Louis Stokes Cleveland VA Medical Center and/or its designee(s). It provides guidance on Health and Human Services (HHS) regulations for the protection of human research subjects at 45 CFR part 46 related to the review and reporting of (a) unanticipated problems involving risks to subjects or others (hereinafter referred to as unanticipated problems); and (b) adverse events. In particular, this guidance clarifies that only a small subset of adverse events occurring in human subjects participating in research are unanticipated problems that must be reported under 45 CFR part 46.

Clinical Investigations of Devices under Investigational Device Exemption (IDE) Regulations require:

- Investigators to submit to the reviewing IRB and the sponsor a report of any unanticipated adverse device effect (UADE) occurring during an investigation as soon as possible, but in no event later than 5 working days after the investigator first learns of the effect (§ 812.150(a)(1)).
- Sponsors or their designees must immediately conduct an evaluation of a UADE, and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

3. Definition/Background

In the case of devices, the Sponsor and/or its designee should evaluate any unanticipated adverse device effect immediately [21 CFR 812.46 (b)] and report the results to the FDA, IRB and participating investigators, if applicable, within 10 working days after the Sponsor and/or its designee first receives notice of it [21 CFR 812.150 (b)(1)]. If the Sponsor and/or its designee determines that an unanticipated adverse device event presents an unreasonable risk to study subjects, the Sponsor will terminate part or all the investigation as soon as possible, but no later than 5 working days after the Sponsor made the determination and no later than 15 working days after the Sponsor first received notice of the effect [21 CFR 812.46 (b)(2)]. Sponsors must receive FDA and IRB approval to resume a terminated study of a significant risk device [21 CFR 812.46(c)].

A Serious Adverse Event (SAE) is generally defined as 'any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, *whether or not considered related to the subject's participation in the research'.* SAE reporting is in accordance with the following regulatory requirements and industry guidelines:

Title 21 CFR 803, Subpart B - Generally Applicable Requirements for Individual Adverse Events Reports
Title 21 CFR 812, Subpart G - Records and Reports
Title 21 CFR 812.140 - Investigational Device Exemptions - Records
Title 21 CFR 812.150 - Investigational Device Exemptions - Reports
ICH GCP Consolidated Guideline - Part 4.11 Safety Reporting

4. Procedure

<u>Determinations about cause</u>

Adverse events may be caused by one or more of the following:

(1) the procedures involved in the research;
(2) an underlying disease, disorder, or condition of the subject; or
(3) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by the device or procedures would be considered related to participation in the research.

<u>Determinations about relatedness</u>

Determinations about the relatedness of adverse events to participation in research likely fall along a continuum between 'definitely related' to the research and 'definitely unrelated'. The Office of Human Research Protections (OHRP) considers 'possibly

related' to participation in the research to be an important threshold for determining whether a particular adverse event represents an unanticipated problem. OHRP defines 'possibly related' as having a reasonable possibility that the adverse event may have been caused by the procedures involved in the research.

Many individual adverse events occurring in the context of research are not related to participation in the research and, therefore, do not meet the second criterion for an unanticipated problem and do not need to be reported under the HHS regulations 45 CFR part 46.103(a) and 46.103(b)(5).

Determination of degree (Serious)

OHRP considers adverse events that are unexpected, related or possibly related to participation in research, and serious to be the most important subset of adverse events representing unanticipated problems. With this understanding, the sponsor and/or its designees will monitor investigators' documented study activities and the regulatory files to assess for the need for potential corrective actions to protect the safety, welfare, or rights of subjects, at a frequency no less than annually. The sponsor will compel Investigators to report events that are (a) unexpected; (b) related or possibly related to participation in research; and (c) serious, to the Research Office and to designee regulatory affairs staff within 5 days of learning of the event.

Other adverse events that are unexpected and related or possibly related to participation in the research, but not serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. Regulatory Affairs staff will monitor such events and report to the IRB and to the Data and Safety Monitoring Board (DSMB), Medical Monitoring Committee (MMC), Clinical Advisory Group (CAG) or similar if any, as required at the local level.

OHRP defines serious adverse event as any adverse event that:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

Reporting of internal adverse events

If the investigator determines that the internal adverse event represents an unanticipated problem, the investigator must report it promptly to the IRB (45 CFR 46.103(b)(5)) according to the reporting guidelines set by the local authority, and simultaneously to the sponsor. The sponsor will periodically monitor study files to ensure that the investigator(s), upon becoming aware of an internal adverse event, has fully assessed whether the adverse event necessitated reporting to various regulatory bodies and was reported accordingly.

Regardless of whether the internal adverse event is determined to be an unanticipated problem, the monitor will compel the investigator(s) to report to the monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC), if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.

If the investigator determines that an adverse event is not an unanticipated problem, but the subsequent monitoring determines that the adverse event does, in fact, represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the sponsor will report this to the FDA within its study progress or final reports, as most appropriate per study timing. The sponsor will also require that the IRB (45 CFR 46.103(b)(5)) of authority be notified.

Reporting of external adverse events

The Sponsor and/or its designee(s) will be required to report external adverse events experienced by subjects enrolled in multicenter clinical trials only to IRB's of authority, but not to Federal and oversight agencies. The external adverse events should be reported only to investigators and IRBs at all participating multicenter institutions when a determination has been made that the events meet the criteria for an unanticipated problem. The sponsor shall forward any reports of external adverse events to the investigator(s) for assessment and determination of whether it rises to a level for IRB reporting.

External adverse event reports received by investigators shall be retained in the investigators' regulatory files for review in accordance with a monitoring plan described in the IRB-approved research plan.

Reporting of other unanticipated problems (not related to adverse events)

Upon becoming aware of any other incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem by applying the criteria described herein. If the investigator determines that the

incident, experience, or outcome represents an unanticipated problem, the investigator must report it promptly to the IRB (45 CFR 46.103(b)(5)).

For multicenter research protocols, if a local investigator at one institution engaged in the research independently proposes changes to the protocol or informed consent document in response to an unanticipated problem, the investigator should consult with the Louis Stokes Cleveland VA Medical Center or its designee regarding the proposed change. The Sponsor will make the determination as to whether the change is required and allowable.

Reporting unanticipated problems to Office of Human Research Protections (OHRP) and supporting agency heads (or designees)

Unanticipated problems occurring in research covered by OHRP-approved assurances FWA00004231 VAMC - Louis Stokes Cleveland, and FWA 00004354, Cleveland VA Med Rsch & Education Fdn, must also be reported by the institution to the supporting Health and Human Services (HHS) agency head (or designee) and OHRP (45 CFR 46.103(a)). The IRB chairperson or administrator, or another appropriate institutional official identified under the institution's written IRB procedures, will be responsible for reporting unanticipated problems to the supporting HHS agency head (or designee) and OHRP. Louis Stokes Cleveland VA Medical Center, as Sponsor, will summarize such reports in its study progress or final reports to FDA.

For multicenter research projects, only the institution at which the subject(s) experienced an adverse event determined to be an unanticipated problem (or the institution at which any other type of unanticipated problem occurred) must report the event to the supporting agency head (or designee) and OHRP (45 CFR 46.103(b)(5)). Louis Stokes Cleveland VA Medical Center, as Sponsor, and/or its designee will summarize these reports to FDA, as well.

1. During protocol development, Louis Stokes Cleveland VA Medical Center or its contracted designee(s) will establish definitions for adverse events, serious adverse events and /or unanticipated adverse device effects in the body of the protocol according to the disease or condition under study and the current regulatory requirements.
2. The importance and process of the investigator's medical evaluation, documentation and reporting of adverse events, serious adverse events and unexpected adverse drug/device effects may be presented at investigator meetings and/or site initiation visits.
3. Information collected will be documented.
4. Should the AE meet 'serious' criteria, be determined to be unexpected, or require immediate reporting by the reviewing IRB, Louis Stokes Cleveland VA Medical Center or its designee(s) will be notified as soon as possible, but no later than 5 working days of the site learning of the event. In the case of a death, the Sponsor will require sites to notify the responsible investigator, the principal investigator, the regulatory affairs specialist(s), and Office of the ACOS

(Associate Chief of Staff) for Research by fax or telephone immediately. Notification should be made to a regulatory affairs specialist in the department or Center conducting the research, e.g., the APT Center, the FES Center, other).

5. The monitor or other Sponsor designee will ensure a copy of any correspondence / reports to or from the reviewing IRB be submitted to the Sponsor, the Research Office, and/or its designee, by fax or by Inter-office mail within 5 working days of learning of the event. Additional reporting of all serious unexpected adverse events will be made in writing to the FDA within 5 working days.
6. All Adverse Event (AE), Serious Adverse Event (SAE) and Unexpected Adverse Device Effects (UADE) reports may be reviewed by the DSMB/MMC/CAG, the IRB, and the Research Office and will be included in any annual reports to FDA.
7. The Louis Stokes Cleveland VA Medical Center study staff or that of its designee(s) will review all unexpected SAEs against the protocol and ICF template to determine if additional risk information should be added. If a determination is made that the protocol and ICF should be revised, a supplement to the study will be made and possibly submitted to the FDA (applicable per FDA rules for device reporting) and all reviewing IRBs within 10 working days of the determination.

5. Definitions

Sponsor: Louis Stokes Cleveland VA Medical Center, Medical Research Service, or a contracted entity under which such research services are provided.

Adverse event: The HHS regulations at 45 CFR part 46 do not define or use the term adverse event, nor is there a common definition of this term across government and non-government entities. Louis Stokes Cleveland VA Medical Center as sponsor uses the term very broadly and includes any event meeting the following definition:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, external adverse events are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, internal adverse events are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered internal adverse events.

Possibly related to the research: There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)).

Serious adverse event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

(Modified from the definition of serious adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

Unanticipated problem involving risks to subjects or others: Any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to a subject's participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Unexpected adverse event: Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling; or
- the expected natural progression of any underlying disease, disorder, or condition of the affected subject(s) and the subject's predisposing risk profile for the adverse event.

(Modified from the definition of unexpected adverse drug experience in FDA regulations at 21 CFR 312.32(a).)

The phrase ‘unanticipated problems involving risks to subjects or others’ is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6. Reference.

Unanticipated Problems Involving Risks & Adverse Events Guidance (2007) | HHS.gov;

Adverse Event Reporting to IRBs - Improving Human Subject Protection, Guidance Clinical Investigators, Sponsors, and IRBs (fda.gov)

7. Rescission:

Sponsor Adverse Event Unanticipated Problems Reporting – Device HSP-023 dated January 1, 2011 was rescinded. Review date for this policy is June 2, 2025.

8. Follow up Responsibility:

Investigator(s)/co-investigator(s) and, when delegated by the investigator(s) with permission of the Sponsor, also sub-investigator(s) and clinical research staff. Designated individuals who monitor sites and those named as responsible for performing Data Management and Regulatory Affairs by the Sponsor, Louis Stokes Cleveland VA Medical Center.